Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts

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Note: The authors have worked to ensure that all information in this book concerning drug dosages, schedules, and routes of administration is accurate as of the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice advance, however, therapeutic standards may change. For this reason and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of a physician who is directly involved in their care or in the care of a member of their family.

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Chapter 15

Use of Tricyclics and Monoamine Oxidase Inhibitors in the Treatment of PTSD: A Quantitative Review

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Posttraumatic stress disorder (PTSD) has a lifetime prevalence of 1% in the general population (Helzer et al. 1987) and a 15% prevalence among Vietnam combat veterans (Kulka et al. 1990). Yet, study of the rational use of psychotropic agents for the treatment of PTSD is in its infancy. Although many different pharmacological agents have been tried, no one drug of choice or pharmacological treatment strategy has yet emerged. The most commonly used medications for the treatment of PTSD are antidepressants. However, results of treatment outcome have been varied across published reports. Clearly, antidepressants are not "curative" in PTSD, and they do not appear to treat all aspects of the disorder.

Nonetheless, by nearly all reports, antidepressants do appear to have some beneficial effects in the treatment of patients with PTSD. However, the extent to which these drugs affect com-

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monly occurring adjunctive symptoms of depression and anxiety versus specific PTSD symptoms is currently unclear. Furthermore, it is not known whether all three core symptom clusters (i.e., reexperiencing, avoidance, hyperarousal) in PTSD respond equally to these medications. The precise delineation of the symptoms that do respond to antidepressants in PTSD is an important next step in establishing a rational approach to pharmacotherapy of the traumatized patient. Analogously, in the schizophrenia literature, the finding that neuroleptics are useful for "positive" rather than "negative" symptoms has lead to more precise pharmacotherapy for the schizophrenic patient.

The present report is a summary of our attempt to synthesize and critically evaluate outcome findings across all published reports (Birkhimer et al. 1985; Bleich et al. 1986; Davidson et al. 1987, 1990; Falcon et al. 1985; Hogben and Cornfield 1981; Kauffman et al. 1987; Kosten et al. 1991; Lerer et al. 1987; Levenson et al. 1982; Milanes et al. 1984; Reist et al. 1989; Shen and Park 1983; Shestatzky et al. 1988; Walker 1982) on the use of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) in the treatment of PTSD. The specific aim was to determine whether antidepressants differentially influence particular PTSD symptoms, or instead primarily treat comorbid major depression and anxiety disorders such as panic disorder.

Given the high clinical demand for information about the role of pharmacotherapy in the treatment of PTSD, and the relative confusion of the literature, we felt it important to provide a more rigorous analysis than is usually achieved through a standard literature review. Several meta-analytic techniques have been developed for the purpose of quantitative literature review (Landman and Dawes 1982). However these techniques, which require calculating statistical effect sizes, are more appropriately utilized in evaluating literatures with numerous controlled studies. In the PTSD literature only 4 out of 15 reports on antidepressant treatment are randomized placebo-controlled trials, while the rest are open trials and case reports.

Because we felt it important to evaluate all published studies, including case reports, standard meta-analytic techniques could not be meaningfully utilized. To perform the analysis, we first evaluated the extent to which factors such as study design, type

of medication, and duration of treatment were related to reports of antidepressant efficacy in PTSD. Next, subjects from all published reports were pooled and rated with a uniform rating scale designed to assess the efficacy of antidepressant medications on particular symptom clusters. This procedure allowed all subjects reported in the literature to be evaluated as one overall sample using identical criteria for symptom improvement. Symptom improvement in all patients was rated on both the primary DSM-III-R (American Psychiatric Association 1987) symptom clusters of PTSD (i.e., reexperiencing, avoidance, and hyperarousal) and symptoms of depression and anxiety. Depression and anxiety symptoms were rated because, although not formally part of the DSM-III-R criteria for PTSD, they often are present in patients with PTSD. Furthermore, given the well-known efficacy of antidepressants in the treatment of depression and panic disorder, it is possible that antidepressants primarily affect these co-occurring symptoms rather than the core symptoms of PTSD. Statistical analysis was performed to determine the relative effectiveness of TCAs and MAOIs on the above-mentioned symptom clusters and to address methodological considerations relevant to the determination of treatment outcome.

METHODS

All published primary data papers dealing with psychopharmacological treatment of chronic (i.e., duration of more than 6 months) PTSD were included for analysis ($N = 15$ studies). Studies were evaluated for study design, drop-out rate, type of medication, comorbid psychiatric diagnoses, method of symptom assessment, range of dosage, duration of treatment, and symptom improvement. Fisher's exact probability test was used to determine whether aspects of study methodology (i.e., study design, use of structured vs. clinical ratings, duration of treatment) were related to overall symptom improvement. For these analyses each drug study was considered separately. All subjects in a particular study were considered as one group, and overall drug efficacy for that study was rated as "good to very good" if there was a greater than 50% reduction of symptoms.

Data analysis was also performed on symptom improvement data from the total pool of individual subjects. Summing across these studies, the total number of subjects was 215 (209 war-related cases, 6 civilian cases). Using the total pool of subjects, we compared the relative efficacy of MAOIs and TCAs on five symptom clusters: 1) reexperiencing (e.g., intrusive memories, nightmares, flashbacks); 2) avoidance (e.g., efforts to avoid reminders of the trauma, detachment, diminished interest, restricted affect); 3) hyperarousal (e.g., insomnia, anger, hypervigilance, physiological reactivity); 4) depression (including neurovegetative symptoms if specified); and 5) anxiety (including panic). The relative efficacy of TCAs and MAOIs on overall global improvement was also determined. Global improvement or improvement on a particular symptom cluster was judged to be good to very good if there was a 50% or greater improvement, to be moderate if there was a 20% to 50% improvement, and to be poor if there was less than 20% clinical improvement. Whenever possible, symptom improvement was rated for each individual. In larger studies that did not include anecdotal descriptions or data from individual subjects, we considered the mean improvement of all patients in that study for data analysis. This determination was made by comparing baseline scores of structured interview data with scores following antidepressant treatment. Subjects dropping out from any study prior to the end of 2 weeks of treatment were not included in data analysis. Symptom improvement was assessed by the consensus of two raters (SMS and RY). A third rater (ELG) then assessed the same studies independently. Interrater reliability using intraclass r was performed by correlating the consensus ratings of the experienced raters with the independent ratings of the third rater. Reliability was established as $r = 0.90$ for reexperiencing, $r = 0.76$ for avoidant, $r = 0.79$ for hyperarousal, $r = 0.88$ for depression, and $r = 0.68$ for anxiety. Chi-square analysis was used to compare the relative efficacy of TCAs and MAOIs.

RESULTS

The published literature to date on antidepressant trials in the treatment of chronic PTSD is summarized in Table 15–1. The

literature, in total, consists of four case reports, seven open trials, and four randomized, placebo-controlled drug trials. Thirteen percent of the subjects were reported to have dropped out because of side effects. The total remaining number of subjects across studies was 128 for TCAs and 87 for MAOIs. The TCAs used included imipramine, desipramine, amitriptyline, and doxepin. Phenelzine was the only MAOI used. Ten of the 15 studies documented a relatively high incidence of comorbid psychiatric diagnoses, including major depression, dysthymia, generalized anxiety, panic, substance abuse, and character disorders. Diagnostic comorbidity was not specified in the other five studies.

When open trial and case studies were compared with ran-

Table 15–1. Studies, subject numbers, and drop-out rates used in analyzing pharmacological treatment of chronic PTSD

Study	Design	TCA	MAOI	Dropouts
Hogben and Cornfeld (1981)	Case	—	5	NR
Levenson et al. (1982)	Case	—	1	NR
Walker (1982)	Case	—	3	2
Shen and Park (1983)	Case	—	3	NR
Milanes et al. (1984)	Open	—	10	4
Birkhimer et al. (1985)	Open[a]	15	5	NR
Falcon et al. (1985)	Open	17	—	NR
Bleich et al. (1986)	Open	25	2	NR
Davidson et al. (1987)	Open	—	10	1
Kauffman et al. (1987)	Open	8	—	0
Lerer et al. (1987)	Open	—	22	3
Shestatzky et al. (1988)	RCT	—	10	3
Reist et al. (1989)	RCT	18	—	6
Davidson et al. (1990)	RCT	22	—	3
Kosten et al. (1991)[b]	RCT	23	19	6
		128	87	28

Note. TCA = tricyclic antidepressant; MAOI = monoamine oxidase inhibitor; NR = not reported; RCT = randomized clinical trial.
[a]Retrospective study.
[b]Preliminary findings reported in Frank et al. 1988.

domized clinical trials, there were no significant differences in overall global symptom improvement (Fisher's exact test, $P = 0.28$). Seven of the 15 studies used structured symptom assessments to measure symptom changes in response to medication, while 8 of the studies used clinical ratings. Overall global symptom improvement was not significantly different in studies using structured symptom ratings (Fisher's exact test, $P = 0.18$).

Most studies used roughly equivalent doses of antidepressants. Doses ranged from 140 to 225 mg/day (mean = 181 mg) for TCAs and 30 to 75 mg/day (mean = 60 mg) for phenelzine. Duration of treatment ranged from 4 to 24 weeks (mean = 10 weeks) for TCAs and from 2 to 8 weeks (mean = 5.8) for phenelzine. To study the effect of treatment duration on global symptom improvement, the 15 studies were divided into those with treatment durations of greater than or less than 8 weeks. There was a nonsignificant trend for greater global improvement in studies with treatment duration greater than 8 weeks (Fisher's exact test, $P = 0.08$).

Monoamine oxidase inhibitors were judged to be better overall than TCAs ($\chi^2 = 33.2$; df = 2; $P < 0.0001$; see Table 15–2). A good to very good global response was reported in 82% of phenelzine-treated patients and 45% of patients treated with TCAs. However, the response of individual symptom clusters to TCAs and MAOIs was less robust than the overall global response (Table 15–2).

The only specific PTSD symptom cluster that showed good improvement in response to antidepressants was the "reexperiencing" cluster (Table 15–2). Overall, phenelzine was found to be significantly more effective than TCAs for this symptom cluster ($\chi^2 = 18.6$; df = 2; $P < 0.001$). On the other hand, symptoms of avoidance tended to respond moderately or poorly to antidepressants. In this case, TCAs were also found to be somewhat inferior to phenelzine. Similarly, symptoms of hyperarousal responded in the moderate to poor range for phenelzine. Hyperarousal was seldom rated in TCA studies.

The adjunctive symptoms of depression and anxiety also showed a poor response to antidepressants. In this case, phenelzine was significantly less efficacious than TCAs for depression ($\chi^2 = 18.6$; df = 2; $P < 0.001$), with only 13% of phenelzine-treated

Table 15–2. Efficacy of antidepressants on global symptom improvement and individual symptom clusters associated with PTSD

	Frequency (%)	
	TCA	**MAOI**
Global		
Good	45	82
Moderate	25	2
Poor	30	16
Not rated	0	0
Reexperiencing		
Good	22	41
Moderate	42	41
Poor	36	11
Not rated	0	6
Avoidant		
Good	0	0
Moderate	20	36
Poor	47	43
Not rated	33	22
Hyperarousal		
Good	4	9
Moderate	23	23
Poor	5	40
Not rated	69	28
Depression		
Good	13	0
Moderate	25	13
Poor	43	62
Not rated	20	25
Anxiety		
Good	11	1
Moderate	0	43
Poor	45	37
Not rated	45	20

Note. The data represent assessments of drug responses from subjects pooled across 15 antidepressant trials: 128 subjects received TCAs, and 87 subjects received phenelzine. Response to medication was judged good if symptoms improved by greater than 50%, moderate if there was between a 20% and 50% improvement, and poor if symptom improvement was less than 20%.

subjects showing a moderate response of depressive symptoms, and 38% of TCA-treated subjects showing a moderate or better response (Table 15–2). Depression was not rated in one-quarter of the studies. The response of anxiety symptoms, including panic, was in the moderate or better range in 44% of patients following phenelzine treatment, compared with 11% with TCA treatment. These symptoms were not rated in many of the studies.

DISCUSSION

The present analysis suggests that antidepressants are useful in the treatment of PTSD, but only for some symptoms. These symptoms are not necessarily the ones for which antidepressants are commonly prescribed. Although global improvement was reported as good to very good in most studies, analysis of particular symptom clusters revealed that only the "reexperiencing" cluster showed significant improvement. Approximately 75% of the subjects showed moderate or better improvement in flashbacks, nightmares, and intrusive traumatic memories, with phenelzine being more effective for these symptoms than TCAs. Symptoms of avoidance and hyperarousal responded poorly to both phenelzine and TCAs. However, within the hyperarousal cluster, symptoms of insomnia showed moderate improvement. In this regard, it should be noted that the efficacy of antidepressants for symptoms of hyperarousal and avoidance was not specified in all studies, likely because marked improvement was not observed.

Interestingly, concurrent symptoms of depression and anxiety (including panic) also failed to respond to antidepressants. This is surprising because antidepressants are very effective in treating major depression and panic disorder in non-PTSD populations. Furthermore, the hypothesis has been raised that antidepressants enhance global improvement in PTSD because of their effect on comorbid major depressive disorder (Davidson et al. 1985; Friedman 1988) and/or panic disorder (Davidson et al. 1985). However, our results suggest that global improvement in PTSD cannot be attributed to the effects of antidepressants on these concurrent disorders. Rather, in addition to their effects on

reexperiencing symptoms, antidepressants may in part improve global functioning through effects on other areas of functioning such as social relationships, family, and work (Giller et al. 1988b), areas that were not systematically evaluated in these studies. It is also possible that global improvement was rated relatively high despite minimal effects on most symptom clusters, because for this chronic and often treatment-resistant population, improvements in even one symptom cluster make a substantial difference in the patient's overall presentation.

In addition to pooling subjects across all studies for the purpose of comparing the efficacy of TCAs with that of MAOIs, we also compared some relevant aspects of methodology between studies. These analyses were performed to explore the relative effect of methodological differences on overall treatment outcome and to confirm the appropriateness of pooling subjects across studies. Treatment outcome did not appear to differ depending on type of study design when the four randomized clinical trials were compared with all open trials. This is largely due to methodological differences within the randomized clinical trials. The two studies using a standard double-blind, placebo-controlled design rated global efficacy as good to very good (Davidson et al. 1990; Kosten et al. 1991). These studies also used a relatively large number of subjects in their experimental groups (i.e., Kosten et al. 1991, $n = 42$; Davidson et al. 1990, $n = 22$) and assessed symptom improvement at the end of an 8-week trial. In the other two studies (Reist et al. 1989; Shestatzky et al. 1988) that reported moderate to poor global improvement, fewer subjects were utilized, and symptom improvement was assessed following 4-week trials. In these studies, poor drug effect may have been related to the significant effect of time alone (i.e., nonspecific or placebo) on improvement.

Our analysis did show a trend toward symptom improvement with greater treatment duration. Patients treated for 8 weeks or longer tended to show greater overall symptom improvement, suggesting that antidepressant treatment trials in PTSD may need to be longer than the standard 4 to 6 weeks recommended for major depression. In Bleich et al.'s study, for example, an 85% response rate to amitriptyline occurred only after 6 months of treatment (Bleich et al. 1986). In fact, it may be that antidepres-

sants should be taken chronically as maintenance medication t prevent relapse, as has been described for chronic depressio (Giller et al. 1988a). The optimal course of antidepressant trea ment for PTSD has not yet been established and awaits furthe assessment through follow-up and medication discontinuatio studies.

When comparing global improvement in studies using star dardized scales versus subjective clinical ratings, no difference were observed. However, some of the standardized scales use in these studies were designed to assess depression and anxiet and as a result may have been too insensitive to detect changes i PTSD-specific symptoms. Furthermore, studies that did use standardized instrument to assess PTSD symptoms typicall used the Impact of Event Scale (Horowitz et al. 1972), a self-r port measure, which may be less sensitive than a clinician-rate instrument.

Issues pertaining to subject heterogeneity could not be a sessed in the present study. For example, we were unable t address systematically the interaction between baseline sym tomatology at treatment onset and symptom improvemer across studies. Nor were we able to identify a subgroup of s verely symptomatic individuals for the purpose of comparin treatment efficacy. In general, inpatients tend to be more severel ill than outpatients. However, in some studies, hospitalizatio status was not clearly stated, or was not considered as a separa variable in data analysis. Nonetheless, an informal assessme indicated that global symptom improvement seemed to be bett in studies using outpatients (Davidson et al. 1990; Kosten et a 1991), compared with those using inpatients. Furthermore, ana ysis of the drop-out data in one study indicated that patients wh were unable to tolerate antidepressant treatment had the highe baseline scores (Davidson et al. 1987). Thus, it may be that sym toms in the moderate, rather than the severe, range of sympto severity are best targeted by antidepressants. Moreover, the rel tively poor improvement in inpatients may reflect comorbi illnesses in these groups such as affective and personality diso ders (Davidson et al. 1985; Helzer et al. 1987; Kulka et al. 199 Yehuda et al. 1990).

Another important issue is the relationship between diagno

tic comorbidity and treatment outcome. The rate of diagnostic comorbidity across pharmacological studies was high, which is in agreement with nonpharmacological studies in PTSD (Davidson et al. 1985; Kulka et al. 1990). This variable was not systematically considered in our analysis because most studies did not specify comorbid diagnoses or indicate whether symptom improvement was related to the occurrence of concurrent psychopathology. The effect of a comorbid diagnosis may in fact affect global symptom improvement with antidepressants. For example, Kosten et al. (1991), in their study of PTSD patients who did not meet the criteria for major depressive disorder, reported the highest rate of symptom improvement among subjects in the randomized clinical trials. Similarly, Davidson et al. (1990), in their study, showed that recovery rates with amitriptyline were generally lower in patients who met diagnostic criteria for concurrent major depressive disorder. In this regard, it is important to note that the studies reviewed in this analysis did not typically distinguish depressive from melancholic symptoms in patients. Thus, the efficacy of antidepressants for PTSD patients with concurrent melancholia is a question that requires further exploration.

The major treatment implication from the above findings is that antidepressants are best prescribed for particular target symptoms of PTSD, especially the reexperiencing cluster, rather than for the entire syndrome as a whole. Patients who suffer from symptoms of avoidance and hyperarousal may be more effectively treated with other agents. For example, in an ongoing open trial on the efficacy of fluoxetine in PTSD, significant improvement in avoidance and hyperarousal has been observed (McDougle et al. 1991). Other drugs that have been reported to be useful in alleviating some PTSD symptoms include clonidine and propranolol for hyperarousal symptoms (Kolb et al. 1984), carbamazepine and lithium for impulsivity and aggressive behavior (Kitchner and Greenstein 1985; van der Kolk 1983), and benzodiazepines for anxiety (van der Kolk 1983). Thus, in the pharmacotherapy of PTSD, different agents may be useful for treating different symptom clusters; furthermore, a combination of pharmacological agents may prove useful in the same patient (Thomson et al. 1990).

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